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EFFECTIVENESS OF RUTAN IN CORRECTING DISORDERS OF LIPID PEROXIDATION IN PREPUBERTAL RATS WITH ACUTE TOXIC HEPATITIS

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Abstract: Considering the increasing incidence of toxic liver damage—the primary organ for xenobiotic detoxification—the insufficient effectiveness of currently used pharmacological treatments necessitates the search for and implementation of new effective drugs for treating hepatobiliary system pathology in prepubertal patients. In this context, the authors studied the effects of Rutan and Karsil on the levels of lipid peroxidation products (Acylhydroperoxides [AcGP], malondialdehyde [MDA]) and the activity of antioxidant enzyme systems (catalase [CAT], superoxide dismutase [SOD]) in the liver during acute hepatitis induced by carbon tetrachloride in one-month-old rats. Results showed that Rutan, similarly to Karsil, reduces elevated levels of AcGP and MDA in the microsomal-cytosolic liver fraction significantly increased by acute toxic hepatitis induced by carbon tetrachloride. Notably, this effect is accompanied by increased activity of antioxidant enzyme systems. It was concluded that Rutan may be used in the treatment of acute liver diseases in the prepubertal period.

Keywords: acute toxic hepatitis, rats, prepubertal period, liver, free radical oxidation, antioxidant defense enzymes.

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Introduction

The widespread prevalence and high incidence of hepatitis present a serious medico-social problem for healthcare systems. The use of many effective hepatoprotectors—derivatives of amino acids and other organic acids, vitamin preparations, and compounds from various chemical groups—is widely discussed globally [1]. In the development of toxic liver pathology, free radical processes play a significant role [2]. One of the current problems in hepatology remains the development and implementation of new highly effective hepatoprotectors, as toxic liver disease incidence has increased in recent years [3,4]. At the same time, the use of known therapeutic agents does not always yield the desired results. It is believed that improving the effectiveness of pharmacotherapy for hepatobiliary system pathologies requires a comprehensive approach using safe multifunctional hepatoprotectors that protect hepatocytes from damage and restore their function. The most promising in this regard is the use of phytopreparations, characterized by a broad spectrum of pharmacological activity, high effectiveness at early stages of diseases, during slow-progressing and chronic diseases, as well as in remission and rehabilitation periods [1,5,6].

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Furthermore, hepatoprotective agents of plant origin used in complex pharmacotherapy potentiate the effects of basic medications and correct metabolic disturbances in the damaged organ [7,8]. This problem is particularly relevant in pediatric practice, as the incidence of acute hepatobiliary diseases in children tends to increase [9]. Previously, we demonstrated the effectiveness of Rutan—an interferon inducer—in treating acute and chronic inflammation in experimental models [10,11]. Considering that liver damage of toxic etiology involves aseptic inflammation in its pathogenesis, it was hypothesized that Rutan might exert hepatoprotective effects. Studies in adult animals confirmed the hepatoprotective properties of Rutan [12]. However, the potential use of Rutan as a treatment for hepatitis in prepubertal subjects remained unexplored. It was also assumed that the antioxidant properties of Rutan's polyphenols underlie its beneficial effects [13].

Aim of the Study

To evaluate the effectiveness of Rutan compared to Karsil on the intensity of lipid peroxidation processes and the activity of antioxidant enzymes in acute toxic hepatitis in the prepubertal period.

Materials and Methods

The study was conducted on 30 white growing rats of both sexes, one month old, born under vivarium conditions. The experiments were carried out in accordance with the rules adopted by the International Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes (Strasbourg, 1986). The conduct of experimental research on laboratory animals was approved by the Ethics Committee of the Tashkent Medical Academy under the Ministry of Health of the Republic of Uzbekistan (protocol No. 9 dated May 26, 2025).

Acute toxic hepatitis (ATH) was induced in the rats by intragastric administration of a 50% oil solution of carbon tetrachloride (CCl_4) at a dose of 0.2 ml/100 g once daily for 4 days. Twenty-four hours after the last administration of CCl_4, the animals were divided into four groups. Rats in the first and second groups received Rutan at doses of 25 mg/kg and 50 mg/kg, respectively; the third group received Karsil at a dose of 40 mg/kg; and the fourth group was left untreated (control relative to all other groups). The drugs were administered once daily for six days.

The effects of Rutan and Karsil on the intensity of lipid peroxidation (LPO) processes and the activity of antioxidant enzyme systems (AOS) in rats were studied. Twenty-four hours after the last procedure, under light ether anesthesia, the rats were sacrificed in a cold room at a temperature of 0–2°C by instantaneous decapitation. The liver was homogenized in a glass homogenizer with a Teflon pestle in an isolation medium consisting of 0.25 M sucrose, 0.05 M KCl in a 0.05 M Tris-HCl buffer solution, pH 7.4.

To precipitate nuclei, mitochondria, and particles of damaged cells, the homogenates were centrifuged at 9000 g for 20 minutes. In the microsomal-cytosolic fraction of the liver, the content of acylhydroperoxides (AcGP) was determined by the method of Gavrilov V.V. and Mishkorudnaya M.M., and the content of malondialdehyde (MDA) by the method of

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Andreeva L.I. [14]. The state of antioxidant enzyme systems (AOS) was assessed by the activity of catalase (CAT) [14] and superoxide dismutase (SOD) [14].

The obtained data were statistically processed using the standard software package Statistica for Windows by the well-known method of variation statistics with evaluation of significance of the indicators (M±m) and differences between samples by Student's t-test. Differences between groups were considered significant at a 95% confidence level ($p < 0.05$).

Results and Discussion

It is well known that the formation of free radicals, which have a destructive effect on the structure of biological membranes of cells, including hepatocytes, is one of the important pathogenetic mechanisms of the damaging action of hepatotoxins [15–17]. This especially applies to carbon tetrachloride [15–17]. The latter is widely used in experimental hepatology in the study and introduction of new hepatoprotectors. Many researchers use the determination of initial products — acylhydroperoxides (AcGP) and intermediate products — malondialdehyde (MDA) of lipid peroxidation to assess the intensity of free radical processes [6,14,18].

In this regard, we investigated the content of AcGP and MDA in prepubertal animals with acute toxic hepatitis treated with Rutan and Karsil. The results of biochemical studies showed a significant increase in LPO products in animals with acute toxic hepatitis. Compared to intact animals, the AcGP content increased more than 4.5 times, and MDA — 3.7 times. These results confirm the high prooxidant activity of carbon tetrachloride [19,20].

In contrast, administration of Rutan at a dose of 25 mg/kg resulted in a decrease of AcGP levels by 68.6% and MDA by 64.0% compared to untreated animals. Doubling the dose of the drug did not lead to a noticeable change in this effect. Experimental pharmacotherapy with Karsil, as seen from the data in Table 1, had a similar effect, i.e., the drug significantly reduced the levels of AcGP and MDA to a degree not significantly different from the results of Rutan.

Table 1.

The effect of Rutan and Karsil on the intensity of lipid peroxidation processes in the liver of rats with acute toxic hepatitis, (M±m, n=6).

Animal groups	Doses, mg/kg	Acyl hydroperoxide rel. units / mg protein	Malondialdehyde nmol/mg protein
Intact	-	0,75 ± 0,04	0,69 ± 0,06
OTG+H_2O	-	3,41 ± 0,23[a]	2,56 ± 0,28[a]
OTG+Rutan	25	1,07 ± 0,08[a,б]	0,92 ± 0,09[б]
OTG+Rutan	50	1,28 ± 0,12[a,б]	1,17 ± 0,11[a,б]
OTG+Karsil	40	1,19 ± 0,13[a,б]	1,08 ± 0,09[a,б]

Note: a – P <0.05 compared to the intact group, b – P <0.05 compared to the control group.

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Therefore, the results of the conducted studies indicate that in acute toxic hepatitis (ATH), there is a significant and persistent increase in the content of lipid peroxidation (LPO) products in the microsomal-cytosolic fraction of the liver. Experimental therapy with Rutan and Karsil led to a substantial decrease in the levels of Acylhydroperoxides (AcGP) and Malondialdehyde (MDA), indicating suppression of LPO intensity.

It is known that the content of lipid peroxidation products depends on the activity of antioxidant enzyme systems (AOS). Taking this into account, we studied the effect of Rutan and Karsil on the activity of antioxidant enzymes in the liver of animals with hepatitis.

The results showed that six days after the induction of the hepatitis model, the activities of catalase (CAT) and superoxide dismutase (SOD) decreased by 64.9% and 60.7%, respectively, compared to the values of healthy animals (Table 2). In the experimental therapy with Rutan at doses of 25 and 50 mg/kg in rats with ATH, a statistically significant increase in CAT activity was observed at 131.9% and 97.9%, and SOD activity at 122.1% and 103.2%, respectively, compared to untreated animals. A similar increase in the activity of the studied enzymes was observed with Karsil therapy, with CAT activity increasing by 140.4% and SOD by 111.6% compared to untreated animals.

It should be noted that with treatment by both drugs, the activity of the studied enzymes did not differ statistically significantly from the corresponding values of healthy animals.

Table 2.

Effect of Rutan and Karsil on the activity of antioxidant enzyme systems in the liver of rats with acute toxic hepatitis (M±m, n=6).

Animal groups	Doses, mg/kg	Catalase, nmol H_2O_2/min · mg protein	Superoxide dismutase conventional units/min · mg protein
Intact	-	1,34 ± 0,12	2,42 ± 0,14
OTG+H_2O	-	0,47 ± 0,04[a]	0,95 ± 0,04[a]
OTG+Rutan	25	1,09 ± 0,11[б]	2,11 ± 0,19[б]
OTG+Rutan	50	0,93 ± 0,19[б]	1,93 ± 0,19[б]
OTG+Karsil	40	1,13 ± 0,10[б]	2,01 ± 0,16[б]

Note: a – P <0.05 compared to the intact group, b – P <0.05 compared to the control group.

Analysis of the results studying the effects of Rutan and Karsil on the activity of antioxidant enzyme systems (AOS) allows concluding that the tested drugs restore the enzymatic activity of catalase (CAT) and superoxide dismutase (SOD), resulting in a clear reduction of lipid peroxidation (LPO) intensity. The obtained results correspond with data from other researchers [10,11]. At the same time, the pharmacological efficacy of Rutan does not significantly differ from that of Karsil.

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Thus, the results of experimental studies on the efficacy of Rutan in correcting disorders of free radical lipid oxidation in prepubertal rats with acute toxic hepatitis (ATH) show that the studied polyphenol-containing compounds suppress the intensity of free radical lipid peroxidation in biological membranes by increasing the activity of AOS enzymes, confirming the hepatoprotective activity of these compounds. Therefore, like Karsil, Rutan can be recommended as a pathogenetic treatment option for toxic liver injuries of various etiologies in pediatric practice.

Conclusions

1. In prepubertal animals, ATH is accompanied by a significant enhancement of LPO processes in hepatocyte biological membranes, which is manifested by an increased content of LPO products in the microsomal-cytosolic liver fraction.
2. The increased intensity of free radical lipid oxidation in ATH in growing animals is accompanied by a decrease in the activity of AOS enzymes in liver cells.
3. Experimental therapy of ATH with Rutan more effectively reduces the intensity of free radical lipid oxidation in the liver compared to Karsil.
4. The positive influence on the activity of antioxidant enzymes allows recommending Rutan for complex treatment of many pathological conditions and diseases in whose pathogenesis enhanced free radical oxidation during the prepubertal period may be a contributing factor.

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